REMARKS

The Office Action of August 13, 2003, has been received and reviewed. Claims 41-46 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claims 41-44 and 46 stand rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Bramson *et al.* Claim 45 stands rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Bramson *et al.* in view of Esandi *et al.* Claims 41 and 42 have been canceled without prejudice or disclaimer. The applicants expressly reserve the right to prosecute all of the prior claims, including claim 41 and 42, in subsequent applications. The applicants respectfully submit that the previously presented claims, including claims 41 and 42, are patentably distinct over the art of record, however to expedite prosecution of the application, the applicants have amended claim 43 to be an independent claim and canceled claims 41 and 42. Claims 44 and 46 have been amended to depend from claim 43. Applicants submit that the currently pending claims are patentably distinct over the art of record and respectfully request reconsideration and withdrawal of the rejections.

Applicants submit that the amendment merely cancels claims and presents a formerly dependent claim as an independent claim. Furthermore, the amendment places the claims in condition for allowance and/or reduces the issues for appeal. Therefore, the applicants respectfully request entry of the amendment.

Support for claim amendments and newly added claims:

Applicants have rewritten formerly dependent claim 43 to include the elements of former independent claim 41. Claims 44 and 46 have merely been amended to reflect proper dependency. Thus, no showing of support is believed to be required for claims 43-46.

Support for claims 47-49 can be found throughout the specification, for example, in paragraph 75.

Rejection under 35 U.S.C. § 112, first paragraph:

Claims 41-46 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking

enablement commensurate with the scope of the claims. To expedite prosecution of the present application, the applicants have canceled claims 41 and 42, without prejudice or disclaimer, and expressly reserve the right to reinstate the subject-matter of these claims in a continuation application. Thus, to the extent that the rejection applies to claims 41 and 42, it is rendered moot and no further comment is necessary. Nevertheless, the arguments of record and those presented herein are applicable to such claims as well as pending claims 43 through 49.

The Office contends that "[t]he critical issue for whether the claimed invention is enabled concerns whether sequentially administering two adenoviral vectors reactive to the same type of antibody (preferably the same type of vector) could circumvent pre-existing [or induced] immunity for repeated [subsequent] adenoviral vector administration in gene therapy" (page 3 of Paper 16). Thus, the Office appears to acknowledge that if the administration of a first adenoviral vector, which raises an antibody response, can be followed by a subsequent administration of an adenoviral vector having a gene of interest to produce a therapeutic effect, despite the induced immunity, the claims are enabled.

Prior to the present invention, several authors believed that neutralizing antibodies (Nab) would be an obstacle to successful gene therapy (*see* the specification at paras. 21 and 22), and indeed the present invention provides an unexpected concept in view of this art (for example, Parks *et al.*, Kass-Eisler, Mack and Mastrangeli *et al.*).

However, contrary to the Office's position, the specification enables a person of ordinary skill in the art to practice the present invention. First, the specification, for example, in paragraph 23, describes literature suggesting that the presence of Nab does not inhibit gene transfer. Second, the experiment conducted by Bramson *et al.* was designed to test whether the presence of Nabs prevented transfer of the gene of interest into the desired tissue in mice. Bramson *et al.* demonstrated that the presence of Nabs does not prevent therapeutic efficacy of the transgene. Hence, Bramson *et al.* and other references support the specification's showing that the presence of Nab does not prevent gene transfer. Third, and most importantly, the working examples in the specification provide clear evidence that indeed efficient gene transfer into the desired tissue is observed in the presence of even high titers of Nab (for example, at

paragraph 77 and FIG. 1). Although there was lower gene transfer to the liver and spleen, transfer to these organs was not completely prevented, even in the presence of high titers of Nab. Moreover, the specification, for example, at paragraph 87, demonstrates that even in the contralateral tumor transgene activity was observed! Thus, the specification demonstrates that an adenoviral vector had traveled through the body of the rat, irrespective of the presence of high titers of Nab, and had infected cells at sites distant from the site of administration. Thus, the present specification demonstrates that even in the presence of high Nab titers, the administration of an adenoviral virus, containing a gene of interest, was sufficient to deliver the virus to other parts of the body. Furthermore, this administration produced therapeutic effects at a sites completely unrelated to the site of administration. Finally, the specification demonstrates that induction of high titers of Nab protects from IL-3 related side effects and virus mediated cellular toxicity, without preventing therapeutic effect.

Therefore, the specification provides working examples, actual data, showing that the administration of a first adenoviral vector, which raises an antibody response, can be followed by a subsequent administration of an adenoviral vector having a gene of interest to produce a therapeutic effect, despite the induced immunity. Further, inducing immunity reduces virus induced cellular toxicity. Therefore, the specification demonstrates, by way of working examples (actual data), "[t]he critical issue for whether the claimed invention is enabled," (page 3 of Paper 16). Thus, the guidance provided by the specification enables a person of ordinary skill in the art to practice the claimed invention.

The Office alleges that the applicants have not responded to the issues raised by Parks *et al.*, Kass-Eisler, Mack and Mastrangeli *et al.* (page 3 of Paper 16). The applicants were of the opinion that they had responded to this issue previously. However, the applicants hereby expressly state that the enablement issues discussed herein, and in prior responses, demonstrate that the applicants "provide sufficient enabling teachings within the specification for the claimed invention." Thus, the applicants submit that they have provided ample evidence contrary to the teachings of Parks *et al.*, Kass-Eisler, Mack and Mastrangeli *et al.*

In particular, claim 43 is enabled since the specification provides working examples of administering a first dose of adenovirus lacking the gene of interest, administering a second dose (a booster) of adenovirus lacking the gene of interest, raising a neutralizing humoral response to the adenovirus lacking the gene of interest and administering a recombinant adenovirus containing the gene of interest (*e.g.*, luciferase), wherein the neutralizing humoral response is cross-reactive against the recombinant adenovirus containing the gene of interest. For example, paragraph 75 teaches the application of claim 43 in a rat model. Thus, claim 43 is enabled by the specification. Furthermore, the recitations in claims 44 to 49 are supported and enabled by the specification. In particular, at least claim 49 is acknowledged by the Office to be enabled (*see* page 3 of Paper 10).

Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 103(a):

Claims 41-44 and 46 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bramson *et al.* Further, claim 44 stands rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bramson *et al.* in view of Esandi *et al.* Applicants respectfully disagree, for the reasons of record and those presented herein. However, to expedite prosecution of the present application, the applicants have canceled claims 41 and 42, without prejudice or disclaimer, and expressly reserve the right to reinstate the subject-matter of these claims in a continuation application. Thus, to the extent that the rejection applies to claims 41 and 42 it is rendered moot and no further comment is necessary. Nevertheless, the arguments of record and those presented herein are applicable to such claims, as well as, pending claims 43 through 49.

The Office alleges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods taught by *Bramson et al* in humans with a reasonable expectation of success" (page 5 of Paper 16). However, the Office has also found that "the art of record teaches away from the instant claims" (page 3 of Paper 16) and that "[t]he instant specification provides a new concept that is contrary to the existing one" (page 8 of Paper

10). Thus, the Office has stated that the art of record teaches away from the claimed invention.

Because the Office has acknowledged that the art of record teaches away from the claimed invention, it cannot be obvious, as a matter of law (*see W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed Cir. 1983); and MPEP § 2141.02), to apply the methods taught by Bramson *et al.* in humans. Furthermore, Bramson *et al.* conducted their experiments to test the ability of an adenoviral vector to function in the face of Nab. Thus, Bramson *et al.* does not teach increasing the very barrier they were testing for the ability of adenovirus to cross. In contrast, the purpose of Bramson *et al.* (testing the ability of adenovirus to cross the immunity barrier) teaches away from the claimed invention.

More particularly, claim 43, as amended, and dependent claims 44 through 49 now recite "providing the human subject with a second dose of said adenovirus lacking the gene of interest." (emphasis added). Bramson *et al.* does not teach or suggest a second dose or that repeating the administration of adenovirus could further prevent viral dissemination. In Bramson *et al.*, the mice are vaccinated once -and only once- with an adenovirus without insert. In contrast, the present application provides examples (*e.g.*, paras. 51 and 63) where the experimental subjects are immunized twice before administration of the adenoviral vector containing the gene of interest. This second administration results in higher titers of antibodies than taught by Bramson *et al.*, and may be beneficial in further decreasing the side effects of the administration of the adenovirus containing the gene of interest.

Hence, the subject-matter of independent claim 43 is novel and nonobvious over Bramson *et al.* Bramson *et al.* does not teach, suggest or motivate the administration of a second dose of an adenovirus lacking the gene of interest and the art of record, as acknowledged by the Office, teaches away from administration of even one dose to induce an immune response. Because the art of record teaches away from inducing a cross-reactive neutralizing humoral response in a human by administering even one dose of an adenovirus lacking the gene of interest, "providing the human subject with a second dose of the adenovirus lacking the gene of interest" is submitted to be clearly nonobvious.

Information Disclosure Statement:

The applicants submitted an Information Disclosure Statement, mailed May 23, 2001, disclosing US Patent 6,211,160. The USPTO Patent Application Information Retrieval System shows receipt of the Information Disclosure Statement, however applicants have not received confirmation that the reference was considered by the Office. Applicants respectfully request written confirmation that US Patent 6,211,160 has been considered by the Office. Applicants offer to submit an additional copy of the reference upon request by the Office.

CONCLUSION

The applicants respectfully request entry of the amendments contained herein. The amendment does not raise any new issues, but merely rewrites formerly dependent claim 43 to include the elements of former independent claim 41. The applicants submit that the amendments place the claims in condition for allowance and reduce the issues for appeal.

If any questions remain following consideration of the remarks and amendments herein, the Examiner is kindly requested to contact the applicant's representative at the number provided herein.

Respectfully submitted,

G. Scott Dorland, Ph.D.
Registration No. 51,622
Attorney for Applicant(s)
TRASKBRITT, P.C.
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

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